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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,642	12/22/2000	Thomas B. Albrecht	026.00041	4973

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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/748,642	ALBRECHT ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8, 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Claims 6-8 and 14-16 are pending and currently under examination in this application. Claims 1-5, 19-13 and 17-18 were cancelled by Applicant in the communications filed 4/28/2003 and 12/18/2003.

Applicant's response filed 11/07/2005 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 05/04/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112-withdrawn

2. The rejection of Claims 6-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendment to claim 7.

Claim Rejections - 35 USC § 102

3. Claims 6-7 and 14-15 remain rejected under 35 U.S.C. 102(e) as being anticipated by Potter et al. (U.S. Patent 6,015,787) for the reasons of record as set forth in the Action mailed 05/04/2005.

Response to Arguments

4. Applicant's arguments filed 11/07/2005 have been fully considered but they are not persuasive. Potter et al. disclose and claim a method of inhibiting calpain in a cell comprising administering a fusion protein of their invention that is a calpain inhibitor (claim 1) wherein the cell is an HIV infected cell (claim 8) and that "fusion proteins may be used to inhibit activation of NF-.kappa.B regulated viruses, e.g., cytomegalovirus, hepatitis B virus, herpes viruses, adenoviruses, HTLV-I, Sendai virus, human herpes virus 6, and HSV type 1 (see, e.g., Baeuerle, Biochem. Biophys. ACTA 1072:63-80, 1991)" (col. 22, lines 36-42).

Applicant has argued that the introduction, by amendment, of the limitation "of a human cytomegalovirus" in the preamble of claim 7 and the recitation, as a limitation in amended claims 7 and 21, of an inherent biological property of a calpain inhibitor that is "wherein the calpain inhibitor increases levels of p21cip1 whereby viral replication of a human cytomegalovirus is decreased," is sufficient to overcome the outstanding grounds of rejection under 35 U.S.C. 102(e) as being anticipated by Potter et al. (U.S. Patent 6,015,787) (see pg. 4-5 of remarks). However, contrary to this argument, the method Potter et al., as claimed and disclosed, is a method of decreasing levels of functional cellular protease in the cells or the subject by exposing the cells or

administering to the subject a calpain inhibitor wherein the functional cellular protease is calpain and anticipates the instant invention because the patented claims of Potter et al. read on both *in vitro* and *in vivo* embodiments of inhibiting viral replication in a cell by inhibiting a functional cellular protease that is calpain and sets forth that cytomegalovirus is contemplated in the context of the invention.

Applicant's recitation of an inherent biological activity of inhibiting calpain, which is the resultant increase in p21cip1, is merely the recitation of a mechanism of activity of a calpain inhibitor that was not specifically recognized by the prior art. The instant method and the method of Potter et al. share the same active step, which is administering or exposing cells to a calpain inhibitor. Potter et al. disclose an example where their method is used to inhibit HIV viral replication and that cytomegalovirus is contemplated in the context of the invention.

Therefore, Applicant's arguments that Potter et al. do not provide an enabling disclosure (pg. 6) are not persuasive because claim 1 of Potter et al. is presumed valid on its face and because the disclosure of Potter et al. (including examples wherein HIV viral replication is inhibited in vitro) is considered enabling for a method of reducing viral replication in cells.

Claim Rejections - 35 USC § 103

5. Claims 6-8 and 14-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (Reference 1 on PTO form 1449, filed July 19, 2002), Henkart et al. (reference 2 on PTO form 1449, filed July 19, 2002), Kido et al.

(Reference 1 on PTO form 1449, filed December 16, 2004) and deJong et al. 1998 (Antiviral Research, Vol. 39: pp. 141-162) for the reasons of record as set forth in the Action mailed 05/04/2005.

Response to Arguments

6. Applicant's arguments filed 11/07/2005 have been fully considered but they are not persuasive. Applicant has presented arguments, on pg. 6 of the instant remarks, that address the teachings of the Roizman et al., Henkart et al., Kido et al. and de Jong et al. references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant has argued (bottom of pg. 6) that the Roizman et al., Henkart et al., Kido et al. and de Jong et al. references are not properly combinable because one skilled in the art of Roizman et al. would have no reason to look at the Henkart et al., Kido et al. and de Jong et al. references for answers. The intent, of this argument, however, is unclear, because it is not clear what "answers" are being referred to.

Moreover, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one

of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as set forth in the Action mailed 05/04/2005 and reiterated here for Applicant's convenience, Roizman et al. teach "A method for treatment of viral infections makes use of the target proteases disclosed herein which are vital to the viral life cycle" and that "The method of treatment disclosed herein is particularly applicable to the herpes virus simplex subtypes 1 or 2, but will be generally applicable to the herpes family, members of which are known to have extensive DNA homologies. Because of extensive sequence homologies to HSV-1 U.sub.L 26 in other organisms, e.g. cytomegalovirus (U.sub.L 80), Varicella-zoster virus (ORF33), Epstein-Barr virus, these treatment strategies are likely to be broadly applicable to all herpes virus (col. 9, lines 44-64). Roizman et al., therefore, do provide both a suggestion and a motivation to look at the Henkart et al., Kido et al. and de Jong et al. references in order to generally extend the applicability of their method to other members of the herpes viral family that share extensive sequence homology and would be, on that basis, reasonably expected to be effective targets of the disclosed methods of treatment.

Applicant has argued (pg. 6 bridge to pg. 7) that likewise, one skilled in the art of Henkart et al., Kido et al. or de Jong et al. would not have been motivated to look at the other art for answers. Again, the intent, of this argument is unclear, because it is not clear what "answers" are being referred to and there is no way to address what might suggest or motivate one of skill to look for "answers" when those "answers are undefined or described.

Applicant has presented arguments (pg. 7) with regard to the motivation that one of skill in the art would require to combine the cited references and stated that no basis as to why one of skill in the art would have looked to any other references for a calpain inhibitor to treat HCMV has been provided. However, contrary to this argument, as set forth in the Action mailed 05/04/2005, one of ordinary skill in the art would have been motivated to practice a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H in order to inhibit cellular proteases vital to the viral lifecycle so as to provide a treatment for viral infection, because CMV retinitis is associated with HIV infection and the need for developing treatment regimens with improved efficacy was known in the art.

Applicant's arguments that none of the references, individually, teach or suggest the use of a calpain inhibitor to treat HCMV (pg. 7) is argued as if the outstanding rejection was under 35 U.S.C. § 102. However, because the outstanding rejection is under 35 U.S.C. § 103(a), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argument that there is no motivation in the art to use the calpain inhibitors of Henkart et al. to treat anything other than HIV is not persuasive because motivation is provided for the reasons set forth in the Action mailed 05/04/2005 and above.

Applicant argues that none of the references, nor combination thereof, suggests using calpain inhibitors to treat viral replication of HCMV by decreasing the levels of a cellular protease (pg. 7) and that the Kido et al. reference does not provide motivation for this because it relates to HIV. However, contrary to this argument and for the reasons of record set forth in the Action mailed 05/04/2005, the Kido et al. reference is not viewed individually, but as part of all the cited references taken as a whole. Applicant's motivation and a motivation taken from the prior art, to combine the teachings of prior art references, need not be the same.

In the instant case, the prior art as a whole teaches methods of inhibiting herpes viral replication and treating herpes viral infections by inhibiting proteases vital to the herpes viral lifecycle and that these methods are generally applicable to other members of the herpes virus family, including cytomegalovirus and that cellular proteases were known to be proteases that were vital to the lifecycle of enveloped viruses. Applicant's arguments are not persuasive.

Applicant's arguments (pg. 7-8) that the outstanding rejection seems to be employing an "obvious to try" standard and that the combination appears to be based on impermissible hindsight, have been fully considered but are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include

knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, as set forth in the reasons of record and above, motivation is present in the prior art, taken as whole, for the instantly claimed methods.

Applicant's arguments (pg. 8) that there is no suggestion, in de Jong, Kido or Roizman et al, to modify Henkart et al. to treat HCMV, is not persuasive for the reasons of record as set forth in the Action mailed 05/04/2005 and above, which briefly reiterated here consider that the outstanding rejection is made over the combination of references, considered as a whole, not individually or as a subset of the cited references. Likewise, Applicant's arguments drawn to the de Jong and Kido references individually are not persuasive for the reasons set forth previously in this action. In particular, Applicant's characterization of the Roizman et al. reference (pg. 8) as relating only to viral proteases is disputed in light of the teaching of Roizman et al. that sets forth that "target proteases disclosed herein which are vital to the viral life cycle" which does not limit the target proteases taught by Roizman et al. to "viral proteases."

Applicant argues (pg. 8) that even assuming that the combinations of references were proper, the cited combination does not teach or suggest a method where the calpain inhibitor increases levels of p21cip1. However, this argument is not persuasive for the reasons set forth above, which briefly reiterated here consider that Applicant's recitation of an inherent biological activity of inhibiting calpain, which is the resultant increase in p21cip1, is merely the recitation of a mechanism of activity of a calpain inhibitor that was not specifically recognized by the prior art.

7. Claims 8 and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Henkart et al. and deJong et al., as applied above in view of Potter et al. (U.S. Patent 6,015,787) for the reasons of record as set forth in the Action mailed 05/04/2005.

Response to Arguments

8. Applicant's arguments filed 11/07/2007 have been fully considered but they are not persuasive. Applicant's arguments drawn to Henkart et al. and de Jong et al. as not being properly combinable (pg. 8) were addressed previously in this action.

Applicant's argues that (pg. 8) that Henkart et al. and de Jong et al. not teach or suggest a method where the calpain inhibitor increases levels of p21cip1 and that Potter does not overcome these deficiencies. However, this argument is not persuasive for the reasons set forth above, which briefly reiterated here consider that Applicant's recitation of an inherent biological activity of inhibiting calpain, which is the resultant increase in p21cip1, is merely the recitation of a mechanism of activity of a calpain inhibitor that was not specifically recognized by the prior art.

Applicant has also argued (pg. 9) that neither Henkart et al. and de Jong et al. suggest modifying Potter to utilize the particular calpain inhibitors specified in claims 8 and 16 because Potter teaches a fusion protein that must be used to have a portion which will enter the cell and there is no suggestion that Potter could be modified to use a calpain inhibitor alone. However, contrary to this argument, and as set forth in the Action mailed 05/04/2005, one of ordinary skill in the art would have been motivated to practice a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional

cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H in order to decrease the replication (because inhibiting the activation of a virus is inherently inhibiting the replication of that virus) of NF-.kappa.B regulated viruses, including cytomegalovirus, so as to provide a treatment for viral infection because CMV is a major cause of morbidity in HIV infected individuals (as taught by deJong et al.). In particular, Applicant's contention that there is no suggestion in any of the references to use a calpain inhibitor alone (i.e., not a fusion protein) is confusing because Henkart et al. teach methods wherein a calpain inhibitor is used alone.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the claimed calpain inhibitor is "not a fusion protein") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on Monday - Friday, 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 517-272-0811811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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